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ORIGINAL PAPER

Three-component reaction between 5,5-diarylthiohydantoins and acetylenic esters in the presence of trialkyl phosphite

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Abstract The adducts produced in the reaction between trialkyl phosphites and acetylenic esters were trapped by thiohydantoins to produce highly functionalized 5-oxo-2-thioxoimidazolidines and 4,5-dihydro-2-(methylthio)-5-oxoimidazoles in good yields.

Keywords Three-component reaction · Thiohydantoin · Acetylenic ester · Trialkyl phosphite

Introduction

Several classes of drugs are based on the imidazole ring system. 5,5-Diphenyl-2-thiohydantoin derivatives contained in vascular endothelial cells have antiproliferative activity [1]. Hydantoins and thiohydantoins exhibit a wide range of biological activities, including anticonvulsant, antiarrhythmic, anti-inflammatory, and antidiabetic properties, as well as herbicidal and fungicidal activity [2]. The formation of a carbon–nitrogen bond is of importance for the synthesis of nitrogen-containing natural products and biologically active systems [3]. As part of our studies on the development of new routes in heterocyclic synthesis [4–7], we now report an efficient one-pot synthesis of dialkyl 2-(4,4-diaryl-5-oxo-2-thioxoimidazolidin-1-yl) succinates **4** and dialkyl 2-[4,4-diaryl-4,5-dihydro-2-(methylthio)-5-oxoimidazol-1-yl]succinates **5** (Scheme 1).

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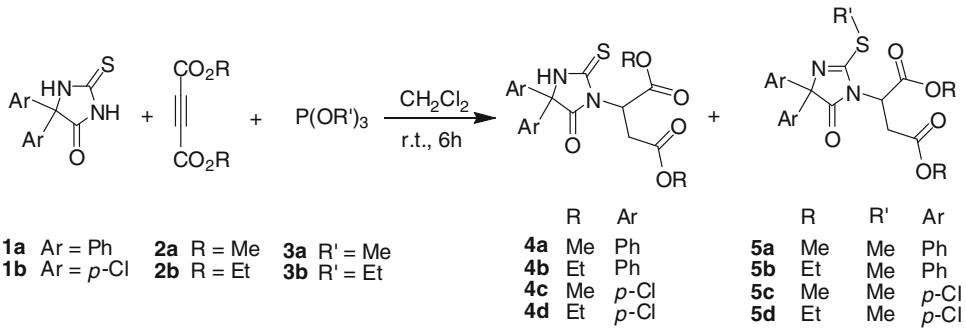
Results and discussion

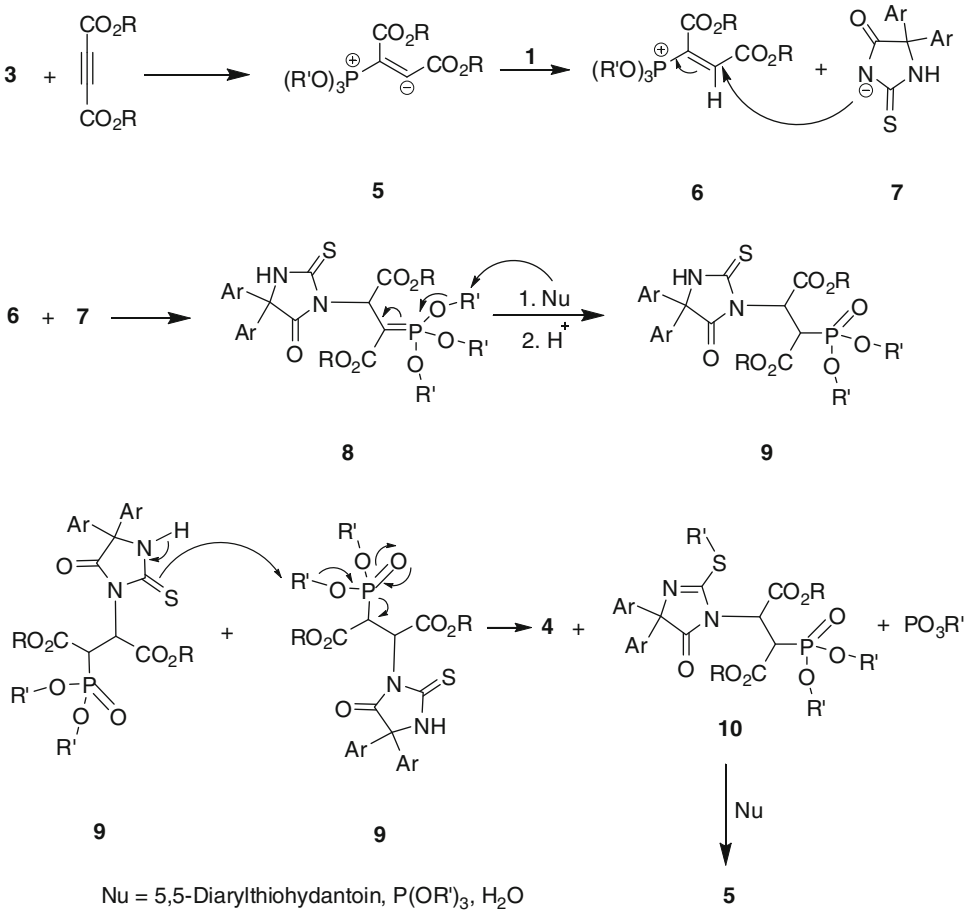
The reaction of dialkyl acetylenedicarboxylates with 5,5-diarylthiohydantoin in the presence of trialkyl phosphite proceeded spontaneously at room temperature (r.t.) in dichloromethane, and was completed within a few hours. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of dialkyl 2-(4,4-diaryl-5-oxo-2-thioxoimidazolidin-1-yl)succinates **4** and dialkyl 2-[4,4-diaryl-4,5-dihydro-2-(methylthio)-5-oxoimidazol-1-yl]succinates **5** (Scheme 1). No product other than **4** and **5** could not be detected by NMR spectroscopy. The structures of compounds **4a** and **5a** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks at $m/z = 412$ and 426. The ^{1}H NMR spectrum of **4a** exhibited a single broad line arising from the NH ($\delta = 10.45$ ppm) of hydantoin; the two protons of the methylene group are diastereotopic and show two characteristic doublet systems at about $\delta = 3.11$ ppm ($J_{AX} = 7.9$, $J_{AB} = 15.9$ Hz) and 3.31 ppm ($J_{BX} = 6.7$, $J_{AB} = 15.9$ Hz); the methine group appears at 5.80 ppm ($J_{AX} = 7.9$, $J_{BX} = 6.7$ Hz). The phenyl residues gave rise to characteristic signals in the aromatic region of the spectrum. Further evidence was obtained from the ^{13}C NMR spectra, which displayed CH–CH_2 carbon resonances at about 30–55 ppm. Partial assignments of these resonances are given in the "Experimental" section.

Although we have not yet established the mechanism of the reaction between trialkyl phosphite and acetylenic esters in the presence of 5,5-diarylthiohydantoin in an experimental manner, a possible explanation is proposed in Scheme 2. Compounds **4** and **5** apparently result from the initial addition of the phosphite to the acetylenic ester and

Scheme 1



Scheme 2



the subsequent protonation of the 1:1 adduct by 5,5-diarylthiohydantoin (Scheme 2).

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [8, 9] it is reasonable to assume that **8** results from initial addition of trialkyl phosphite to dialkyl acetylenedicarboxylates and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion **6** might be attacked by the conjugate base of the NH-acid to form phosphorane **8**. Intermediate **8** with loss of trialkyl phosphate either leads to **4** or it loses a proton and is subsequently methylated to yield **5** (Scheme 2). The structures of the stable crystalline solids **4** and **5** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of these compounds display the correct molecular ion peaks. Any initial fragmentation involved the complete loss of the ester moieties and scission of the heterocyclic ring system.

In conclusion, the reaction of 5,5-diarylthiohydantoin with dialkyl acetylenedicarboxylates in the presence of trialkyl phosphite leads to the facile three-component synthesis of dialkyl 2-(4,4-diaryl-5-oxo-2-thioxoimidazolidin-1-yl)succinates **4** and dialkyl 2-[4,4-diaryl-4,5-dihydro-2-(methylthio)-5-oxoimidazol-1-yl]succinates **5**. The present method has the advantage that not only is the

reaction performed under neutral conditions, but the starting materials can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches [10].

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHNO-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Advance instrument with $CDCl_3$ as solvent at 300.1 and 75.1 MHz. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Isocyanides and dialkyl acetylenedicarboxylates were obtained from Fluka and were used without further purification. 5,5-Diaryl-2-thioxoimidazolidin-4-ones **1** were prepared by known methods [11, 12].

*Typical procedure for the preparation of **4a** and **5a***

To a stirred solution of 0.537 g **1** (2 mmol) and 0.284 g **2a** (2 mmol) in 5 cm^3 dichloromethane was added dropwise a solution of 0.248 g **3a** (2 mmol) in 2 cm^3 CH_2Cl_2 at 5 °C over 10 min. The reaction mixture was then allowed to warm to room temperature and stand for 6 h. The solvent was removed under reduced pressure and the residue was separated by silica column chromatography (Merck 230-400 mesh) using *n*-hexane/AcOEt as eluent to afford **4a** and **5a**.

Dimethyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)-butanedioate (**4a**, $C_{21}H_{20}N_2O_5S$)
White powder; yield 0.39 g (47%); m.p.: 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.11$ (1 H, dd, (AB)X system, $J_{AX} = 7.9$, $J_{AB} = 15.9$ Hz, CH), 3.31 (1 H, dd, (AB)X system, $J_{BX} = 6.7$, $J_{AB} = 15.9$ Hz, CH), 3.55 (3 H, s, MeO), 3.70 (3 H, s, MeO), 5.80 (1 H, dd, $J_{AX} = 7.9$, $J_{BX} = 6.7$ Hz, CH), 7.35–7.51 (10 H, m, CH), 10.45 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.8$ (CH_2), 51.7 (MeO), 52.0 (CH), 52.9 (MeO), 78.8 (C), 127.5 (2 CH), 127.8 (2 CH), 128.0 (2 CH), 128.2 (2 CH), 128.5 (CH), 128.6 (CH), 140.8 (C), 141.0 (C), 161.4 (OC=O), 168.7 (OC=O), 170.2 (NC=O), 180.7 (C=S) ppm; IR (KBr): $\bar{\nu} = 3{,}425$ (NH), 1,740 (C=O), 1,452 (C=C) cm^{-1}; MS (70 eV): $m/z = 412$ (M^+, 18), 351 (75), 292 (78), 267 (60), 166 (100), 77 (32), 59 (12).

Diethyl 2-(5-oxo-4,4-diphenyl-2-thioxoimidazolidin-1-yl)-butanedioate (**4b**, $C_{23}H_{24}N_2O_5S$)
White powder; yield 0.40 g (45%); m.p.: 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (3 H, t, $^{3}J_{HH} = 7.1$ Hz, Me), 10.15 (3 H, t, $^{3}J_{HH} = 7.1$ Hz, Me), 3.15 (1 H, dd, (AB)X system, $J_{AX} = 8.4$, $J_{AB} = 16.5$ Hz, CH), 3.37 (1 H, dd, (AB)X system, $J_{BX} = 6.3$, $J_{AB} = 16.5$ Hz, CH), 4.02–4.29 (4 H, (AB)X_3 system, 2 CH_2O), 5.79 (1 H, dd, $J_{AX} = 8.4$, $J_{BX} = 6.3$ Hz, CH), 7.25–7.58 (10 H, m, CH), 10.41 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$ (Me), 14.5 (Me), 34.0 (CH_2), 51.9 (CH), 61.6 (CH_2O), 62.7 (CH_2O), 78.8 (C), 127.5 (2 CH), 127.6 (2 CH), 128.1 (2 CH), 128.2 (2 CH), 129.4 (CH), 129.5 (CH), 140.2 (C), 140.8 (C), 161.1 (OC=O), 168.1 (OC=O), 170.3 (NC=O), 180.7 (C=S) ppm; IR (KBr): $\bar{\nu} = 3{,}426$ (NH), 1,740 (C=O), 1,453 (C=C) cm^{-1}; MS (70 eV): $m/z = 441$ (M^+, 8), 367 (62), 267 (66), 166 (100), 77 (42), 73 (15).

Dimethyl 2-[4,4-bis(4-chlorophenyl)-5-oxo-2-thioxoimidazolidin-1-yl]butanedioate
(**4c**, $C_{21}H_{18}Cl_2N_2O_5S$)
White powder; yield 0.43 g (45%); m.p.: 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 3.09 (1 H, dd, (AB)X system, $J_{AX} = 8.4$, $J_{AB} = 16.8$ Hz, CH), 3.30 (1 H, dd, (AB)X system, $J_{BX} = 6.0$, $J_{AB} = 16.8$ Hz, CH), 3.62 (3 H, s, MeO), 3.72 (3 H, s, MeO), 5.77 (1 H, dd, $J_{AX} = 8.4$, $J_{BX} = 6.0$ Hz, CH), 7.25–7.45 (10 H, m, CH), 10.45 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.9$ (CH_2), 51.7 (MeO), 51.8 (CH), 52.8 (MeO), 78.1 (C), 129.3 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 180.5 (C=S) ppm; IR (KBr): $\bar{\nu} = 3{,}425$ (NH), 1,740 (C=O), 1450 (C=C) cm^{-1}; MS (70 eV): $m/z = 481$ (M^+, 20), 421 (72), 335 (75), 234 (100), 111 (28), 59 (10).

Diethyl 2-[4,4-bis(4-chlorophenyl)-5-oxo-2-thioxoimidazolidin-1-yl]butanedioate
(**4d**, $C_{23}H_{22}Cl_2N_2O_5S$)
White powder; yield 0.43 g (42%); m.p.: 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (3 H, t, $^{3}J_{HH} = 7.1$ Hz, Me), 1.16 (3 H, t, $^{3}J_{HH} = 7.1$ Hz, Me), 3.08 (1 H, dd, (AB)X system, $J_{AX} = 8.5$, $J_{AB} = 16.5$ Hz, CH), 3.30 (1 H, dd, (AB)X system, $J_{BX} = 6.0$, $J_{AB} = 16.5$ Hz, CH), 4.02–4.34 (4 H, (AB)X_3 system, 2 CH_2O), 5.80 (1 H, dd, $J_{AX} = 8.5$, $J_{BX} = 6.0$ Hz, CH), 7.29–7.46 (10 H, m, CH), 10.40 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (Me), 14.4 (Me), 34.6 (CH_2), 52.0 (CH), 61.6 (CH_2O), 62.8 (CH_2O), 77.4 (C), 129.3 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 180.5 (C=S) ppm; IR (KBr): $\bar{\nu} = 3{,}426$ (NH), 1,740 (C=O), 1,453 (C=C) cm^{-1}; MS (70 eV): $m/z = 509$ (M^+, 16), 435 (78), 335 (72), 234 (100), 111 (25), 73 (22).

Dimethyl 2-[4,5-dihydro-2-(methylthio)-5-oxo-4,4-diphenylimidazol-1-yl]butanedioate (**5a**, $C_{22}H_{22}N_2O_5S$)
White powder; yield 0.36 g (42%); m.p.: 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.73$ (3 H, s, MeS), 3.09 (1

H, dd, (AB)X system, $J_{AX} = 8.3$, $J_{AB} = 16.4$ Hz, CH), 3.25 (1 H, dd, (AB)X system, $J_{BX} = 6.4$, $J_{AB} = 16.4$ Hz, CH), 3.55 (3 H, s, MeO), 3.68 (3 H, s, MeO), 5.08 (1 H, dd, $J_{AX} = 8.3$, $J_{BX} = 6.4$ Hz, CH), 7.25–7.56 (10 H, m, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.8$ (Me), 33.9 (CH_2), 51.7 (MeO), 51.8 (CH), 52.8 (MeO), 78.5 (C), 127.5 (2 CH), 127.7 (2 CH), 128.0 (2 CH), 128.1 (2 CH), 128.5 (CH), 128.6 (CH), 140.9 (C), 141.0 (C), 161.2 (OC=O), 168.4 (OC=O), 170.2 (NC=O), 180.6 (C=S) ppm; IR (KBr): $\bar{\nu} = 1{,}743$ (C=O), 1,574 (C=N), 1,444 (C=C) cm^{-1}; MS (70 eV): $m/z = 426$ (M^+, 12), 411 (28), 281 (55), 166 (100), 77 (35), 59 (20).

Diethyl 2-[4,5-dihydro-2-(methylthio)-5-oxo-4,4-diphenylimidazol-1-yl]butanedioate
(**5b**, $C_{24}H_{26}N_2O_5S$)
White powder; yield 0.34 g (38%); m.p.: 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.09$ (3 H, t, $^3J_{HH} = 7.1$ Hz, Me), 1.15 (3 H, t, $^3J_{HH} = 7.1$ Hz, Me), 2.73 (3 H, s, MeS), 3.05 (1 H, dd, (AB)X system, $J_{AX} = 8.1$, $J_{AB} = 16.7$ Hz, CH), 3.31 (1 H, dd, (AB)X system, $J_{BX} = 6.4$, $J_{AB} = 16.7$ Hz, CH), 4.01–4.26 (4 H, (AB)X_3 system, 2 CH_2O), 5.02 (1 H, dd, $J_{AX} = 8.0$, $J_{BX} = 6.4$ Hz, CH), 7.20–7.56 (10 H, m, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (Me), 14.1 (MeS), 14.4 (Me), 34.6 (CH_2), 52.0 (CH), 61.6 (CH_2O), 62.8 (CH_2O), 78.8 (C), 127.6 (2 CH), 127.8 (2 CH), 128.1 (2 CH), 128.2 (2 CH), 128.7 (CH), 128.8 (CH), 140.4 (C), 140.5 (C), 161.1 (OC=O), 168.1 (OC=O), 170.3 (NC=O), 180.9 (C=S) ppm; IR (KBr): $\bar{\nu} = 1{,}740$ (C=O), 1,574 (C=N), 1,449 (C=C) cm^{-1}; MS (70 eV): $m/z = 455$ (M^+, 16), 439 (25), 281 (61), 166 (100), 77 (40), 73 (20).

Dimethyl 2-[4,4-bis(4-chlorophenyl)-4,5-dihydro-2-(methylthio)-5-oxoimidazol-1-yl]butanedioate
(**5c**, $C_{22}H_{20}Cl_2N_2O_5S$)
White powder; yield 0.39 g (40%); m.p.: 106–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.72$ (3 H, s, MeS), 3.09 (1 H, dd, (AB)X system, $J_{AX} = 8.4$, $J_{AB} = 16.8$ Hz, CH), 3.30 (1 H, dd, (AB)X system, $J_{BX} = 6.0$, $J_{AB} = 16.8$ Hz, CH), 3.62 (3 H, s, MeO), 3.72 (3 H, s, MeO), 5.01 (1 H, dd, $J_{AX} = 8.4$, $J_{BX} = 6.0$ Hz, CH), 7.25–7.45 (10 H, m, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.7$ (Me), 33.9 (CH_2), 51.7 (MeO), 51.8 (CH), 52.8 (MeO), 78.1 (C), 129.3 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 180.5 (C=S) ppm; IR (KBr): $\bar{\nu} = 1{,}730$ (C=O), 1,581 (C=N), 1,436 (C=C) cm^{-1}; MS (70 eV): $m/z = 495$ (M^+, 10), 479 (75), 349 (65), 234 (100), 111 (24), 59 (15).

Diethyl 2-[4,4-bis(4-chlorophenyl)-4,5-dihydro-2-(methylthio)-5-oxoimidazol-1-yl]butanedioate
(**5d**, $C_{24}H_{24}Cl_2N_2O_5S$)
White powder; yield 0.38 g (36%); m.p.: 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (3 H, t, $^3J_{HH} = 7.1$ Hz, Me), 1.16 (3 H, t, $^3J_{HH} = 7.1$ Hz, Me), 2.72 (3 H, s, MeS), 3.08 (1 H, dd, (AB)X system, $J_{AX} = 8.5$, $J_{AB} = 16.5$ Hz, CH), 3.30 (1 H, dd, (AB)X system, $J_{BX} = 6.0$, $J_{AB} = 16.5$ Hz, CH), 4.02–4.34 (4 H, (AB)X_3 system, 2 CH_2O), 4.99 (1 H, dd, $J_{AX} = 8.5$, $J_{BX} = 6.0$ Hz, CH), 7.29–7.46 (10 H, m, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (Me), 14.1 (MeS), 14.4 (Me), 34.6 (CH_2), 52.0 (CH), 61.6 (CH_2O), 62.8 (CH_2O), 77.4 (C), 129.3 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 180.5 (C=S) ppm; IR (KBr): $\bar{\nu} = 1{,}730$ (C=O), 1,581 (C=N), 1,436 (C=C) cm^{-1}; MS (70 eV): $m/z = 523$ (M^+, 10), 507 (18), 349 (70), 234 (100), 111 (30), 73 (19).

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